Award Number: W81XWH-05-2-0053

TITLE: Comprehensive Reproductive System Care Program – Clinical Breast Care Project (CRSCP-CBCP)

PRINCIPAL INVESTIGATOR: COL Craig D. Shriver, M.D., FACS
Eileen Bronfman, RN

CONTRACTING ORGANIZATION: Henry M. Jackson Foundation for the Advancement of Military Medicine
Rockville, MD 20852

REPORT DATE: September 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
01-09-2007	Annual	21 Apr 2006 – 30 Aug 2007

4. TITLE AND SUBTITLE

Comprehensive Reproductive System Care Program – Clinical Breast Care Project (CRSCP-CBCP)

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-05-2-0053

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

COL Craig D. Shriver, M.D., FACS
Eileen Bronfman, RN

Email: craig.shriver@na.amedd.army.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Henry M. Jackson Foundation for the
Advancement of Military Medicine
Rockville, MD 20852

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The Windber/Walter Reed Clinical Breast Care Project will help lead the way in the 21st century in the crusade against breast disorders. The project will utilize a multidisciplinary approach as the stand of care for treating breast diseases and breast cancer. This multidisciplinary model integrated prevention, screening, diagnosis, treatment and continuing care, but the project is further unique in the incorporation of advanced in risk reduction, informatics, tissue banking and research. These efforts focus on decreasing the morbidity and mortality of breast cancer among American women.

15. SUBJECT TERMS
Tissue Banking, Biomedical Informatics, Focused Research, Translational Research, Genomics, Proteomics, Risk Reduction, Comprehensive Breast Care

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	23	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

Cover.....1

SF 298.....2

Table of Contents.....3

Introduction.....4

Body.....7

Key Research Accomplishments.....12

Reportable Outcomes.....13

Conclusions.....14

References.....17

Appendices.....17

Comprehensive Reproductive System Care Program—Clinical Breast Care Project (CRSCP-CBCP)
Annual Report

1. INTRODUCTION:

The Clinical Breast Care Project (CBCP) is the outcome of the initial FY00 and subsequent Congressional appropriations, and consists of an extensive collaborative effort between Windber Medical Center (Windber, PA – 12th Congressional District of the Honorable John P. Murtha) and Walter Reed Army Medical Center, with funding management by the Henry M. Jackson Foundation for the Advancement of Military Medicine. "The Clinical Breast Care Project (CBCP)" moniker is modified to better reflect its expanded congressional mission, and in FY05 became officially entitled, "The Clinical Breast Care Project of the Comprehensive Reproductive System Care Program" In correspondence, conversation and general usage the shortened form is the "CBCP (of the CRSCP)".

Ultimate Goal of this project: Decrease morbidity and mortality of breast cancer among American Women. Through the interlacing of the five pillars, the CBCP will help lead the crusade against breast disorders.

- Develop a comprehensive breast care center/system that enables health care providers with a multidisciplinary team approach to work toward a common goal.
- Empower women with breast cancer and other breast disorders with the decision-making tools and environment to enhance quality of life and to meet psychosocial needs of the patients and their families.

The five pillars of the CBCP of Walter Reed/Windber are (1) Risk Reduction (2) Focused Research (Genomics and Proteomics); (3) Tissue banking; (4) Biomedical informatics; and (5) Clinical Care.

Pillar Specific Objectives:

1. ***Risk Reduction***:
    - Identify the population of patients at above average risk for the development of breast cancer.
    - Decrease this identified population's rate of breast cancer development.
    - Analyze potential cost differential in the prevention of breast cancer development.
2. ***Focused Research***:
    - Utilize our CBCP-developed panel of microsatellite chromosomal markers to genomically assess various stages of breast disease, malignant and

benign, in our on-going effort to elucidate the biologic development timeline of breast cancer.

- Analyze our in-depth serum and blood repository utilizing various proteomic identification and pattern technologies in our ongoing effort to identify new biomarkers that can be predictive of breast cancer risk and development.
- Utilize our microarray gene expression profiling capabilities in our effort to analyze the gene expression changes of the continuum of breast disease and cancer development.
- Analyze the relationship of certain breast cancer protein aspects, eg. ORP-150 protein, to prognosis and other known variables of breast cancer biology.

3. ***Tissue Bank***:
   - Collect and store specimens of breast tissues, lymph nodes, bone marrow aspirates, serum, blood cells (leukocytes), and plasma from every patient undergoing a breast biopsy and/or breast surgery at WRAMC, WMC, MGMC, and LRMC who consent to participate in this study. Use the power of this tissue bank to dramatically further breast disease research.
4. ***Bio-Informatics***:
   - Develop and implement a clinically-relevant prospective, longitudinal computerized database for use in patients with all types of breast care needs.
   - Link this database information through the Internet to data set at a rural primary breast care center with appropriate security and firewall protections.
   - Develop the database to allow for "on-the-fly," relational, clinically-relevant statistical analysis.
   - Develop an informatics companion to the prospective serum / breast tissue bank. (Pillar 3)
5. ***Clinical Care***:
   - Decrease the negative psychological impact on the patient of having an evaluation or treatment intervention for breast disease.
   - Create and maintain an environment (medical, physical, psychological) conductive to the multiple needs of the patient undergoing breast disease evaluation / treatment.
   - Utilize objective measurement instruments to longitudinally assess the patient's psychological response to evaluation and intervention, and base modifications on those results.

Summary of the methodology of the project.
The five pillars of the CBCP of Walter Reed/Windber are (1) Clinical Care; (2) Tissue banking; (3) Risk Reduction; (4) Biomedical informatics; and (5) Focused research (Genomics and Proteomics).

- The clinical care pillar was established by building state of the art breast care facilities at the Windber and Walter Reed sites. These sites were critical to the ability to implement all other pillars of this Project. The Walter Reed Comprehensive Breast Center opened in July 2001, and the Joyce Murtha Breast Center in Windber opened in February 2002.

- The tissue banking pillar was established at both sites in collaboration and entails acquisitions, storage, and movement amongst the sites for research purposes of tissue garnered from all breast surgeries being preformed at both locations. The robust IRB-approved protocol that enables this pillar is unique in four critical aspects: It is a tissue usage protocol, not a tissue repository protocol. It is hypothesis-generating, not hypothesis-driven research; It allows for patients to pre-consent for secondary, future uses of the tissues in presently-unknown research; It contains a unique fail-safe mechanism to protect the complete diagnostic integrity of all samples.

- The biomedical informatics effort, is a collaborative development effort between Walter Reed, Windber and Inforsense, driving the development of a comprehensive data warehouse storing clinical and molecular data related to breast disease This is a resource for all CBCP investigators and is exportable for use by other investigators, programs, and organ sites. The data warehouse uniquely integrates clinical data with genomic and proteomic analysis of patient samples and is being extended to incorporate an image repository This is being developed in close collaboration with industry leaders in the high-end database field, specifically Inforsense and Concentia Digital. Extensive efforts to model the pathways of breast cancer and its risk factors are underway at Windber with consultation from Walter Reed.

- The risk reduction pillar is a vital portion of this mutual project which has resulted in the capability of the project to establish a screening program to identify women who are at high risk for developing breast cancer, and to enter them into a very time- and resource-intensive risk

reduction program which can only be appropriately resourced through an appropriation such as this, to decrease significantly these patients' chance of getting breast cancer in the future.

The research aspect is centered on functional genomic/microarrays/proteomics analysis of the tissues and biospecimens, which are acquired as described above. The collaborative research on the functional genomics is established through a high-end microarray, genomics, and proteomics facility at the CBCP Windber Research Institute and will be used as the prime research center for the tissue collaborations, which are developed through this project.

- An important outgrowth of this effort is and will be the bringing of more patients into the Windber and Walter Reed sites for breast cancer evaluations and treatment options; also, the economic development at Windber is being enhanced through job creation and establishment of the scientific research center.

2. BODY:

The CBCP established six primary tasks in its approved Statement of Work for the 2006 fiscal year. These six tasks consist of:

- Task 1. Enroll over 500 patients annually to the "Core" CBCP protocols through consenting in the main CBCP clinical sites.
    a. Core protocols of Tissue and Blood acquisition and molecular testing at the DNA, RNA and Protein level, allied with the clinical and demographic databases.

- Task 2. Continuing molecular analysis in CBCP labs, as outlined in the CBCP Core Protocols allowing for global expression analysis of the DNA, RNA and Protein features.
    a. Utilize this repository as the basis for all molecular analysis in CBCP labs, as outlined in the CBCP Core Protocols allowing for global expression analysis of the DNA, RNA, and Protein features.
    b. Utilize this repository as the basis for intramural and extramural collaborations for secondary usage research.

- Task 3: Continuing software development of the CLWS (Clinical Laboratory Workflow System) and its further deployment into the clinical/research arms of the CRSCP-CBCP.

- Task 4. Identifying and counseling no less than 100 high risk patients for development of breast cancer and employ risk reduction strategies.
    a. Perform BRCA gene mutation testing on 10 patients annually in contract with MYRIAD Genetics.

- Task 5. Performing targeted research into genomic analysis of Stages I, II, and III breast cancer, DCIS, LCIS and pre-malignant neoplasia, and presenting findings at national meetings and in peer-reviewed publications.

- Task 6. Perform mass spectrometry fingerprinting of 200 sera samples from patients with diagnosis of breast diseases and analyze for distinct patterns based on disease state.

Task 1: Enrolling over 500 patients in the "core" CBCP protocols.
See section 5 Reportable Outcomes for the breakdown and number of subjects enrolled in "core" CBCP protocols.

Task 2: Continuing molecular analysis in CBCP labs, as outlined in the CBCP Core Protocols allowing for global expression analysis of the DNA, RNA and Protein features. A new organizational plan at the CBCP labs at WRI allowed for more efficient identification of samples to be parallel-processed. As a result, core organizational assets of DNA, RNA, and protein analysis became more robust. This ongoing effort resulted in approximately 200 samples undergoing broad analysis on a molecular level. For FY 2006, **623** donors contributed **5,469** samples. As it is resource-intensive to perform comprehensive molecular profiling even in a project such as CBCP, and cost-prohibitive to perform the comprehensive (DNA, RNA, Protein levels) on all CBCP samples (especially since our success in accruing patients has been so extensive, resulting in our far exceeding our goals for annual specimen acquisitions for the tissue repository), CBCP instead performs certain analyses on important subsets of samples of compelling research interest, and the "global" profiling across the entire Central Dogma (DNA, RNA, Protein) on a different selected subset, in order to maximize efficiencies and appropriately utilize monetary and equipment resources.

Task 3: Continuing deployment of the CLWS (Clinical Laboratory Workflow System) into the clinical/research arms of the CRSCP-CBCP. During the last year, a standard operating procedure (SOP) for data entry and quality assurance (QA) of the questionnaire data has been established. The current QA measures for clinical data include visual inspection by the data entry clerk, double blind-data entry, and a computer program which checks the application of all the QA rules that have been developed to examine the data integrity within and between data fields. An

instruction manual for completing the core questionnaire was developed and distributed to all personnel who gather, review, or enter clinical data. A QA issue tracking (QAIT) system has also been developed and implemented, which dramatically improved the communications on QA issues between the WRI data entry group and the Walter Reed questionnaire QA team. The system is in daily use by both WRI and Walter Reed. Development of the edit utility of the CLWS was completed. Data correction files were compiled and are being applied in a test environment.

With the belief that electronic data capturing will enhance clinical data collection and precision, WRI has taken the initiative in developing a prototype tablet application using the Pathology Checklist as the first example following a decision made at the last CBCP Offsite meeting. This prototype is under further evaluation at both WRI and Walter Reed before a full-blown development starts.

The data warehouse development has further evolved to provide data and analytical support to CBCP research, which is done by collaborating with leading data management and analysis companies such as InforSense and Concentia Digital. An On-Line Analytical Processing (OLAP) tool has been developed to allow for easy access and stratification of hundreds of data elements across thousands of subjects enrolled in CBCP. A 'patient view' tool has been developed to allow for exploration of warehoused data from an individual patient. An application prototype has been developed to enable users to access clinical or experimental images at ease with a built-in robust data-element filtering capability. All these translational research-enabling applications will be migrated to and further developed on a newly designed patient-centric, object-oriented data model with a temporal dimension. We expect that this newly designed data model, which is in the process of being implemented, will dramatically enhance our translational research capability when compared to the old questionnaire-based data structure.

Task 4: Identifying and counseling high risk patients for development of breast cancer and employ risk reduction strategies. The risk reduction pillar is a vital portion of this mutual project which has resulted in the capability of the project to establish a screening program to identify women who are at high risk of developing breast cancer, and to enter them into a very time- and resource-intensive risk reduction program which can only be appropriately resourced through an appropriation such as this, to decrease significantly these patients' chance of getting breast cancer in the future.

A total of 332 patients were entered into the program this year. The extensive risk assessment, family history and pedigree generation, computerized modeling of individual risk, genetic mutation testing when appropriate (BRCA-1 and BRCA-2),

implementation and follow-up of intervention strategies to include chemoprevention, novel diagnostic testing, and even surgical prophylaxis, resulted in a highly successful program where breast cancer truly is being prevented before it ever occurs in many women.

Task 5: Performing targeted research into genomic analysis of Stages I, II, and III breast cancer, DCIS, LCIS and pre-malignant neoplasia, and presenting findings at national meetings and in peer-reviewed publications the period of July 1, 2006 through June 30, 2007. CBCP continues to have tremendous success in this regard. We have verified that important genetic changes occur across multiple chromosomal regions as breast epithelium transitions from non-neoplastic into neoplastic states. We have identified these changes and published the specific markers for chromosomal loci that we identified as having changed during this transition. Whether or not any of these changes are casal in the malignant transformation process remains to be determined. We are considering, as an organization, whether to seek patent protection for this panel of markers, which may be considered a diagnostic and prognostic marker panel for breast cancer and breast cancer development. See ATTACHMENT 2 for the list of publications and presentations.

Task 6: Perform mass spectrometry fingerprinting of 200 sera samples from patients with diagnosis of breast diseases and analyze for distinct patterns based on disease state. In this year we focused our proteomics efforts in applying the new emerging technologies to serum samples to develop the standard methods that will enable the rapid profiling of clinical samples for patient and disease stratification. Alongside the method development, we have also supported the proteomics analysis of breast cancer clinical samples from Hershey Medical College, PA and Loma Linda University, CA. This collaborative research was aimed to look into new sample types to enhance the scope of breast cancer research for CBCP and also to partner with the collaborators for developing grant proposals in the area of breast cancer.

Protein microarrays have gained a lot of popularity recently, especially in profiling the patterns of serum and tissue proteins from the cancer related clinical specimens. To incorporate some of the emerging technologies in this area of proteomics to our core functionalities, we started optimizing the procedures in reading the cytokines and growth factors from the serum through the use of Ray biotech's glass based Antibody Microarrays. With the availability of Genepix array reader (Ray Biotech's G-series chips are compatible with Genepix) in our Genomics facility the optimization of serum samples preparation with the arrays has been possible by reading out the spots for reproducibility between the replicate sample applications within the chip and between the chips.

We have received 50 breast cancer (BC) serum samples from Hershey Medical College for differential proteomics by 2D DIGE. To establish the serum profiles that associate with bone metastases, the sera from BC subjects who developed bonemets and underwent treatment (n=10; progression visit) and sera from the BC subjects with bonemets (n=10) before the pretreatment and, BC subjects without bonemets (n=10) were chosen for 2D DIGE analysis. A pooled sample that represents the respective groups (3groups) was made from each group and the samples were labeled with different cyanine dyes and were run by 2D gel electrophoresis in duplicates. The differentially expressed (39) spots were picked by staining and matching the gel that loaded with unlabeled protein sample to the DIA (differential in gel analysis) processed image spots. We have identified proteins from 10 differentially expressed spots. Among these differentially expressed spots, the IGKC protein expression was very distinct between BC without bonemets (4 fold higher) vs BC with bonemets, and there was not much significant difference between the bonemets groups. We are in discussions with the Hershey Medical college group to extend research further on the samples using the proteomics protocols developed at WRI.

3. ADDITIONAL ACCOMPLISHMENTS

AAMC began accruing patients to the protocol in the first quarter and has consistently contributed to patient accrual throughout the full year period. Challenges regarding constraints to the research process flow, from consenting patients to acquiring, storing and shipping biopsecimens, across multiple and varied departments within the community medical center were resolved collaboratively between Anne Arundel Medical Center staff and Walter Reed Army Medical Center Staff. A smooth flowing process aligned with the research quality goals of the CBCP was fully established in this start-up affiliation by June 30th, 2007. A site visit conducted on 7/16/07 confirmed these findings. In the next year, we expect that Anne Arundel Medical Center will be a well-seasoned operational CBCP partner, actively contributing biospecimens and clinical data of gold standard quality to the CBCP biorepository and biomedical informatics systems.

The CBCP conducted the 7th Annual CBCP Offsite 12 – 15 November 2006. Current state of research was presented by various scientists from WRAMC and WRI. Scientific Advisory Board Meeting and strategic planning was conducted during the sessions and the scientific presentations received much positive feedback from the Scientific Advisory Board.

The project with InforSense to create an On-Line Analytical Processing (OLAP) tool for accessing the CBCP data, has moved forward smoothly as scheduled. The first production version was released to the CBCP on April 17,

2006. This version is being used by the Biomedical Informatics group and the CBCP leaders in both Walter Reed Army Medical Center and the Windber Research Institute. Development with Inforsense has continued and a prototype incorporating a new patient centric data model and a patient event time-line viewer and alignment tools is being tested. The new data model will allow the data warehouse to manage an extensive array of patient data for breast and other diseases.

4. KEY RESEARCH ACCOMPLISHMENTS

- Continued to build the world's largest and best-characterized biospecimen repository of breast disease specimens, now numbering over 26,284 total specimens on over 3,334 enrolled research patients.
- Identified, characterized, and verified the chromosomal changes that occur during the progression of breast tissue from benign to early malignant disease.
- Continued studies of low-abundance proteins and peptides that are found in the bloodstream of patients with breast cancer (i.e., an important step in developing a "breast cancer blood test").
- Used the database and data warehouse system that CBCP has developed for four years, to integrate the clinical, molecular, pathologic, and biorepository aspects of CBCP translational research. It's robust query capability and analysis tools have assisted in stratifying patients populations for our studies. This is leading to having the ability to do in silico science.
- Other developments in the Biomedical informatics core have included development of a new patient centric data model, new tools for microarray data QA, MS data protein peak detection and alignment and an analysis of breast disease co-occurrence.
- A paper Field, L., Love, B., Kane, J., Deyarmin, B., Hooke, J., Ellsworth, R., & Shriver, C. "Differential Gene Expression in Normal Breast Tissue From African American and Caucasian Women") presented at the American Association for Cancer Research Annual Meeting 2007, Los Angeles, CA., was selected for a press conference. This work is part of our ongoing research into the bases of differences in breast cancer outcomes seen between Caucasian and African American women.
- Gene expression analysis of primary (node negative) versus primary (node positive) revealed a 70 gene signature distinguishing two types of tumors.
- Gene expression of primary breast tumors and matched lymph node metastases revealed a metastatic signature of 51 genes.
- 856 specimens have been genotyped with a panel of 26 markers that give insight into the stage and prognosis of the tumors.

- A collaboration with Vanderbilt University to examine proteomics differences associated with lymph node metastasis was initiated and has resulted in the discovery of patterns of protein expression that may distinguish tumors that has lymph node metastasis from those that do not. (See below).

5. REPORTABLE OUTCOMES

The CBCP Research Protocols and number of subjects recruited to each for the period July 1 2006 to June 30 2007 is as follows:

Clinical Breast Care Project Walter Reed Army Medical Center

- Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development - **218**
- Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease - **302**
- Molecular Phenotyping of Bone Marrow Aspirates and Peripheral Blood Collected As Part of The Walter Reed Army Medical Center Clinical Breast Care Project (CBCP) – **81**

The Windber Joyce Murtha Breast Care Center Research Protocols and subjects recruited to each is as follows:

- Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development - 124
- Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease – 95

The Malcolm Grow Medical Center Research Protocols and subjects recruited to each is as follows:

- Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development- 25
- Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease - 11
- A decision to discontinue the protocols at Malcolm Grow Medical Center was made in January 2007. Continuation of the project was not cost effective based on decreased patient volume

The Landstuhl Regional Medical Center Research Protocols and subjects recruited to each is as follows:

- Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development-37
- Collection of serum specimens was also discontinued at Landstuhl Regional Medical Center. Re-evaluation of continuing the project at LRMC proved not cost effective.

Psyco-Social Oncology Services
A dedicated psychologist counseled 54 patients on an ongoing or crisis basis and sees all diagnosed breast cancer patients attending our Friday template. The services provided by this resource are as follows:

- Psycho-social assessment and evaluation of newly diagnosed cancer patients
- For those patients who exhibit a high level of distress, a system has been established that allows close monitoring of patients to include one on one time during chemotherapy.
- Individual and family therapy are available for all breast cancer patients who are in need of support. For patients who live at a distance, telephone sessions are available.
- A Buddy System that provides support to newly diagnosed breast cancer patients from breast cancer patients who have completed treatment.
- On-going psycho-social consultation with patients' medical providers.

Three types of Support Groups are also available:

- A group for patients actively engaged in cancer treatment is provided. The group is a structured 8-week group that meets for 90-minutes once per week. The group format is concrete and offers practical support to patients.
- A group for patients who have completed all treatment. This cancer survivorship group also meets for 8 sessions, 90-minutes, once per week. The format is also concrete and practical.
- A group for parents who have cancer that provides guidance to them to help their children thrive as they overcome cancer. The same format is also used for this group.
- All groups can be conducted in person or via video teleconferencing. Video teleconferencing allows patients who live a distance from Walter Reed, or are too ill to travel a distance, to participate in the support group process.

6. CONCLUSIONS

The next great advances in breast cancer prevention and treatment will be based upon an increased understanding of the changes that occur in the cells of normal breast tissue, as they transition into cancer cells. The CBCP, through its unique and inter-connected 5 pillars, leverages the strengths of its clinical care arm focusing its research arm to study these cells as they change into cancer. To date, we have been the first to show that the way that breast cancer "behaves", is possibly pre-determined very early in the change of the cells as they are becoming cancerous, as opposed to the cancer cells getting "worse" as they grow and develop. In other words, our important findings are indicating that the behavior of the cancer cells is determined in the development of the cancer, not later. The implications of these findings are critical in our understanding of breast cancer biology, and are leading to new

understanding in developing prevention strategies and treatment programs. Our tissue repository has grown into the world's largest and best characterized (annotated) biorepository of human breast tissues, receiving great acclaim from research organizations around the world, and is being shared with other research organizations of great renown, in an effort to speed the pace of discoveries through sharing of this irreplaceable resource. We are finalizing our study into whether or not we can identify "the breast cancer blood test", through the use of serum repository, linked to one of the world's foremost organizations capable of identifying protein patterns in serum from various organ system cancers.

Breast cancer is the most common non-skin cancer in women. It is the single greatest cause of cancer deaths among women under 40, and is a significant cause of mortality for women in the United States Armed Forces. Breast cancer mortality among women <50 years accounts for >40% of years of life lost due to this disease. The economic, social and emotional cost to families is far greater when a young woman dies than when an older woman dies of breast cancer. The more aggressive nature of the disease in young patients along with the attendant costs underscores the importance of early detection of breast cancer in young women. Breast cancer is a curable disease if it is detected early; as such early detection is related to survivorship, cost of treatment and quality of life for the affected woman.

The majority (>90%) of women in active military service are < 40 years of age. The Department of Defense (DOD) with its high percentage of young women and its commitment to health care is particularly concerned about breast cancer. When discovered at a later stage, treatment of breast cancer is expensive, aggressive and results in considerable disruption to the woman's ability to contribute to society. Cost and disruption to life are considerably less when the carcinoma is discovered at an earlier stage. Furthermore, the DOD has a high percentage of African-American (~40%) and Hispanic (~10%) women. Death rates from breast cancer tend to be particularly high in these ethnic groups owing in part to later stage of detection and to the more aggressive nature of breast cancer in these groups.

The active duty military force is approximately 20% female. Most of these service members are in the age range (30-40 years) where routine screening for breast cancer consists only of clinical breast examination. Both mammography and clinical breast examination have a very poor accuracy in the young active duty force in determining which breast abnormalities require treatment, and which are benign and can be left alone.

The immense scale and impact of this problem for the military can be assessed by the fact that there were over 2,000 cases of breast cancer diagnosed in active duty service members over the last ten years (source: ACTURS DoD Tumor Registry data).

Furthermore, there were over 8,000 unnecessary breast biopsies done on active duty women during this time because it takes 4 breast biopsies of normal noncancerous lesions to find each individual breast cancer. Hence, women often need to take lengthy amounts of time off from duty in order to undergo multiple tests leading up to the biopsy as well as time off from duty because of the biopsy itself. This translates into approximately 10,000 weeks, or 30 person-years, of time lost in the evaluation of normal, benign breast lesions in active duty service members. This would be unacceptable for any other healthcare issue, and should be so for this one.

Unfortunately, at the present time there is absolutely no screening tool available currently to diagnose breast cancer in the early, curable stages for women under the age of 40, who make up the vast majority of women in military uniform.

As indicated, approximately 20% of the active duty military force is female, most under the age of 50. Breast cancer strikes one in eight women in her lifetime, and there is a documented change in breast cancer incidence in recent years, such that breast cancer is being detected and diagnosed more often in younger women under the age of 50, and the same is true in our military members. In the same way that diagnostic and therapeutic efforts through the military and US Army are carried out in infectious disease care and research, eg. Malaria, Typhoid, etc., so too must the military address the effects of the scourge of breast cancer and breast diseases on the 20% of total active duty force who are women.

Moreover, CBCP developed and to this day maintains the only specialty breast cancer evaluation and treatment center in the US Army, which is at the CBCP Comprehensive Breast Center at Walter Reed AMC.

Additionally, CBCP is the only Army facility that financially supports direct genetic testing of active duty (all Services) women who are identified in our Center as being in a high risk category of carrying a BRCA genetic mutation, which when present can signify an up to 90% increased risk of breast cancer development.

CBCP Breast Center is the Army-recognized specialty referral center for active duty personnel from around the globe with medical disorders related to all breast diseases and breast cancer. CBCP Breast Center routinely cares for women on active duty Army from places such as Iraq / OIF, Korea, Europe, and the Far East. CBCP annually cares for over 5,000 patients at its site at Walter Reed.

In summary the Clinical Breast Care Project, a collaborative effort between Walter Reed and Windber, has resulted in excellent working relationships and collaborations between the two sites on all five of the project's main pillars. The project continues to achieve its goals and looks forward to further continuance of this great vision and what will be a national resource, into the future.

7. REFERENCES

N/A

8. APPENDICIES

- ATTACHMENT 1 List of personnel receiving pay from the research effort in FY06
- ATTACHMENT 2 : List of publications and meeting abstracts for FY 2006

ATTACHMENT 1

CBCP PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT
July 1, 2006 through June 30, 2007

Last Name	First Name	Role	Percent of Effort
Shriver	**Craig**	**Principal Investigator**	**25%**
Awunor	Angela	Research Nurse	100%
Basham	Janice	Licensed Practical Nurse	100%
Bronfman	Eileen	Administrative Director	100%
Chestang	Allan	Data Manager	100%
Cooper	Leslie	Psychologist	100%
Courville	Faith	Research Nurse	100%
Cronin	Kerri	Receptionist	
Del	Ismail	Data Manager	100%
Fantacone	Jamie Leigh	Pathology Assistant	100%
Glasco	Tiffani	Executive Office Coordinator	100%
Gutchell	Veronica	Head Nurse, CBCP/ Nurse Practitioner	100%
Hafi	Muhammad	Postdoctural Fellow Epidemiology	20%
Hamsher	Carlyle	Research Assistant	100%
Harris	Katie	Research Assistant	100%
Hilton	Karrie	Research Nurse	100%
Hooke	Jeffrey	Head of Pathology	100%
Jama	Yusuf	Research Assistant	100%
Jones	Anita	Research Nurse	100%
Kelley	Kay	Research Protocol Coordinator	100%
Malady	Lori	Staff Research Nurse	100%
Means	Marilyn	Lead Medical Clerk/Receptionist	100%
Miller	Donald	Data Manager	100%
Minohar	Nallini	Research Assistant	100%
Moroni	Maria	Scientist	100%
O'Neill	Stacy	Research Nurse	100%
Pappas	Jennifer	Research Associate	100%
Park	Kathleen	Clinical Nurse Specialist	100%
Patterson	Carol	Medical Assistant	100%
Ponniah	Sathibalan	Scientist-Immunologist	100%
Progar	Christina	Program Administrator	100%

Reece	Heike	Data Manager	100%
Rojas	Winifred	Lab Tech/Phlebotomist	100%
Rosenquist	Monica	Budget Analyst	100%
Russo	Jamie	Staff Research Nurse	100%
Sessoms	Lisa	Protocol Coordinator	100%
Smith	Anna	Research Assistant	100%
Smith	Rosson	Research Nurse	100%
Stojadinovic	Alexander	Breast Surgeon	25%
Storrer	Catherine	Senior Research Associate	100%
Vilakasi	Patricia	Research Nurse	100%
Wardlaw	Margaret	Nurse Practioner	100%
Williamson	Eric	Clinic Administrator	100%
Zhao	Xinyan	Histology Technician	100%
Zhu	Kangmin	Epidemiologist	20%

ATTACHMENT 2

PUBLICATION, ABSTRACT AND PRESENTATION DATA

June 1, 2006 – June 30, 2007

Ellsworth, D., Ellsworth, R., Becker, T., Deyarmin, B., Patney, H., Jordan, R., Hooke, J., & Shriver, C. "Genomic Heritage of Sentinel Lymph Node Metastases: Implications for Clinical Management of Breast Cancer Patients [Poster Presentation]", Poster Presentation at the 43rd American Society of Clinical Oncology Annual Meeting, June 1-5, 2007, Chicago, IL.

Ellsworth, R., Deyarmin, B., Hooke, J., & Shriver, C. "Clinical Implication of the Molecular Relationship Between HER2 and BRCA1 [Poster Presentation]", Poster Presentation at the 43rd American Society of Clinical Oncology Annual Meeting, June 1-5, 2007, Chicago, IL.

Seeley, E., Ellsworth, R., Ellsworth, D., Sanders, M., Hooke, J., Caprioli, R., & Shriver, C. "Identification of Proteins Promoting Development of Metastatic Breast Tumors [Poster Presentation]", Poster Presentation at the 43rd American Society of Clinical Oncology Annual Meeting, June 1-5, 2007, Chicago, IL.

Ellsworth RE, Seeley EH, Ellsworth DL, Hooke JA, Caprioli RM, Shriver CD, "Identification of Protein Expression Differences in Invasive Breast Tumors from African American Compared to Caucasian Women", submitted to SABCS, Jun 2007.

Ellsworth RE, Love B, Hooke JA, Shriver CD, "Identification of Chromosomal Changes Associated with the Transition from *in situ* to Invasive Breast Cancer", submitted to SABCS, Jun 2007.

Ellsworth RE, Deyarmin B, Patney H, Hooke JA, Shriver CD, "HER2 Gene Amplification is a Marker for Global Genomic Instability", submitted to SABCS, Jun 2007.

Ellsworth DL, Seeley EH, Ellsworth RE, Deyarmin B, Sanders ME, Hooke JA, Caprioli RM, Shriver CD, "Tumor Microenvironment in Breast Cancer Metastasis: Direct Tissue Protein Profiling of Tumor-Associated Stroma from Invasive Breast Cancer Patients with versus without Axillary Lymph node Metastasis", submitted to SABCS, Jun 2007.

Ellsworth DL, Ellsworth RE, Patney HL, Becker TE, Deyarmin B, Jordan RM, Hooke JA, Shriver CD, "Primary Tumor Heterogeneity and Sentinel Lymph Node Metastases: Understanding Molecular Processes of Breast Cancer Metastasis", submitted to SABCS, Jun 2007.

Bekash A, Maskery S, Kvecher L, Hooke JA, Liebman MN, Shriver CD, Mural RJ, Hu H, "A Pilot Study of Controversial Breast Cancer Risk Factors Using the Clinical Breast Care Project Database as a Research Environment", submitted to SABCS, Jun 2007.

Maskery S, Hu H, Liebman M, Shriver CD, Verbanac K, Tafra L, Rosman M, "Bayesian Analysis of Recurrence in Lymph Node Positive and Lymph Node Negative Breast Cancer Patients", submitted to SABCS, Jun 2007.

Ellsworth RE, Patney HL, Ellsworth DL, Love B, Hooke JA, Shriver CD," Genomic Discrimination of Metastatic from Non-Metastatic Primary Breast Tumors", submitted to SABCS, Jun 2007.

Ellsworth RE, Hooke JA, Ellsworth DL, Shriver CD, "Contribution of Chromosomal Alterations to the Development of Poorly-Differentiated Invasive Breast Carcinomas", submitted to SABCS, Jun 2007.

Ellsworth RE, Hooke JA, Shriver CD, "Pathological Characteristics of Breast Tumors in African American Women Treated within an Equal-Access Health-Care System: Biological and Molecular Contributions to the Aggressive Phenotype and Poor Clinical Outcomes", submitted to SABCS, Jun 2007.

Maskery S, Hu H, Liebman MN, Hooke J, Shriver CD, Taioli E, "Traditional Breast Cancer Risk Factors and Common Breast Pathologies in Post-Menopausal Women", submitted to SABCS, Jun 2007

Seebach J, Field L, Love B, Hooke J, Ellsworth RE, Shriver, "Identification of a Gene Expression Breast Cancer Metastasis Profile", submitted to SABCS, Jun 2007.

Hu H, Field L, Stegmaier P, Love B, Ellsworth RE, Shriver CD, Liebman MN, Mural RJ, "A Transcription Factor-Centric Computational Analysis of Genes Differentially Expressed in Healthy Breast Tissues from African American and Caucasian Women", submitted to SABCS, Jun 2007.

Field LA, Seebach JF, Love BJ, Deyarmin B, Kane J, Hooke JA, Ellsworth RE, Shriver CD, "Identification of Gene Expression Differences in Primary Breast Tumors from Node-Negative and Node-Positive Women", submitted to SABCS, Jun 2007.

Ellsworth RE, Seeley EH, Ellsworth DL, Sanders ME, Hooke JA, Caprioli RM, Shriver CD, "Identification of Proteins Promoting Development of Metastatic Breast Tumors", submitted to SABCS, Jun 2007.

Ellsworth RE, Deyarmin B, Shriver CD, "Molecular Relationship Between HER2 and BRCA1 in Invasive Breast Carcinoma", submitted to ASCO, Jun 2007.

Ellsworth RE, Shriver CD, "HER2/BRCA1", submitted to SABCS, Jun 2007.

Ellsworth DL, Ellsworth RE, Becker TE, Deyarmin B, Patney HL, Hooke JA, Shriver CD, "Genomic Heritage of Sentinel Lymph Node Metastases: Implication for Clinical Management of Breast Cancer Patients", submitted to SABCS, Jun 2007.

Bronfman L, Shriver CD, Gutchell E, Chapter 2 "The Clinical Perspective", submitted Jun 2007.

Collins PM, "Hidden in Plain View", Navy Medicine, p 24-25, Jun 2007.

Vizza J, Neatrour DM, Felton PM, Ellsworth DL, "Improvement in Psychosocial Functioning During an Intensive Cardiovascular Lifestyle Modification Program", Journal of CR & P, submitted Jun 2007.

Liebman MN, Deyarmin B, Shriver CD, Stegmaier P, Karas H, Kel A, Wingender E, "Analysis of HER2/neu as a Diagnostic/Biomarker Using ExPlain to Examine Signaling Pathways and Transcription Factors", submitted to SABCS, Jun 2007.

Callaghan K, Ellsworth DL, Ellsworth RE, Becker T, Hooke JA, Shriver CD, "Genomic Instability and the Development of Metastatic Lymph Node Tumors", Annals of surgical Oncology, submitted Jun 2007.

Field LA, Love BJ, Hadix JA, Ellsworth RE, Shriver CD, "Identification of Blood-Based Biomarkers for the Detection of Breast Cancer and Lymph Node Status", submitted to SABCS, Jun 2007.

Callaghan KA, Weyandt JD, Ellsworth RE, Shriver CD, "Identification of Genetic Predisposition to Development of Lymph Node Metastasis in Breast Cancer Patients", submitted to SABCS, Jun 2007.

Jordan RM, Hu H, Heckman CM, Kvecher L, Shriver CD, Mural R, Yang YC, "Peripheral Blood Microarray Data May Aid in Predicting Lymph Node Status of Breast Cancer Patients", submitted to SABCS Jun 07.

Yang Y, "Array Based Comparative Genomic Hybridization (aCGH) Technology", submitted to SABCS Jun 2007.

Somiari S, "Letter to the Editor", Int J Cancer, 121, 219-223, Mar 2007.

Ellsworth RE, Ellsworth DL, Love B, Patney HL, Hoffman LR, Kane J, Hooke, JA, Shriver CD, "Correlation of Levels and Patterns of Genomic Instability with Histological Grading of DCIS, Annals of Surgical Oncology, submitted Mar 2007.

Ellsworth DL, Seeley EH, Ellsworth RE, Deyarmin B, Sanders ME, Hooke JA, Caprioli RM, Shriver CD, "Protein Expression Profiles Generated by Histology-Directed MALDI-TOF Differ in Primary Breast Carcinomas from Patients with versus without Axillary Lymph Node Metastasis", AACR, Mar 2007.

Ellsworth RE, Hooke JA, Shriver CD, "Molecular Differences in Breast Tumors from African American and Caucasian Women", AACR Mar 2007

Ellsworth RE, Hooke JA, Field LA, Shriver CD, "Contribution of Genomic Instability to the More Aggressive Form of Breast Cancer in African American Women", AACR Mar 2007

Field LA, Jordan RM, Hadix JA, Dunn MA, Shriver CD, Ellsworth RE, Ellsworth DL, "Functional Identity of Genes Detectable in Expression Profiling Assays Following Globin mRNA Reduction of Peripheral Blood Samples", The Canadian Society of Clinical Chemists, submitted Mar 2007.

Somiari SB, Shriver CD, Heckman C, Olsen C, Hu H, Jordan R, Arciero C, Russell S, Garguilo G, Hooke JA, Somiari RI, "Plasma Concentration and Activity of Matrix Metalloproteinase 2 and 9 in Patients with Breast Disease, Breast Cancer and at Risk of Developing Breast Cancer", Elsevier Ireland Ltd, 2006, p 98-107.

Ellsworth DL, Seeley EH, Ellsworth RE, Deyarmin B, Sanders ME, Cornett DS, Hooke JA, Caprioli RM, Shriver CD, "Direct Tissue Characterization of Protein Expression in Metastatic Breast Cancer". San Antonio Breast Cancer Symposium, Dec 2006

Ellsworth DL, Kostyniak PJ, Gillard D, Love B, Ellsworth RE, Deyarmin B, Hooke JA, Shriver CD, "Abundance and distribution of Persistent Environmental Pollutants in Breast Tissue Following Mastectomy". San Antonio Breast Cancer Symposium, Dec 2006

Somiari SB, Kovatich AJ, Baran PN, Jordan R, Maskery S, Zhang Y, Deyarmin B, Hooke J, Shriver CD, "The Expression of Cell Cycle Regulating Proteins and Steroid Hormone Receptor Status in Invasive Breast Cancer: Association with Tumor Grade and Stage", AACR, April 2007

Ellsworth DL, Seeley EH, Ellsworth RE, Deyarmin B, Sanders ME, Cornett DS, Hooke JA, Caprioli RM, Shriver CD, "Examining Protein Expression Profiles in Axillary Lymph Nodes Using History Directed MALDI-TOF to Identify Markers of Early Metastatic Breast Cancer". AACR 2006

Ellsworth RE, Weyandt JD, Patney HL, Anthony K, Shriver CD, "Identification of cSNPs in Environmental Response Genes Contributing to Breast Cancer Etiology". ASHG Oct 2006
Maskery, S., zhang, Hu, H., Hooke, J., Shriver, & Liebman, M. "Breast Pathology Co-Occurrence in Statified Populations, Implications for Breast Cancer Development in Different Populations" American Association for Cancer Research Annual Meeting, Washington, DC. April 1 - 5, 2006.

Sotiriou C, Wirapati P, Loi S, Harris A, Fox S, Smeds J, Nordgren H, Farmer P, Praz V, Haibe-Kains B, Desmedt C, Larsimont D, Cardoso F, Peterse H, Nuyten D, Buyse M, Van de Vijver MJ, Bergh J, Piccart M, Delorenzi M, "Gene Expression Profiling in Breast Cancer: Understanding the Molecular Basis of Histologic Grade to Improve Prognosis", Journal of the Nat Cancer Instit, Vol 98, No 4, 15 Feb 2006.